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Cutaneous Metastasis In Internal Malignancies

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Abstract: **Skin metastases occur in 0.6%-10.4% of all patients with cancer and represent 2% of all skin tumors. Skin metastases from visceral malignancies are important for dermatologists and dermatopathologists because of their variable clinical appearance and presentation, frequent delay and failure in their diagnosis, relative proportion of different internal malignancies metastasizing to the skin, and impact on morbidity, prognosis, and treatment. Another factor to take into account is that cutaneous metastasis may be the first sign of clinically silent visceral cancer. The relative frequencies of metastatic skin disease tend to correlate with the frequency of the different types of primary cancer in each sex. Thus, women with skin metastases have the following distribution in decreasing order of frequency of primary malignancies: breast, ovary, oral cavity, lung, and large intestine. In men, the distribution is as follows: lung, large intestine, oral cavity, kidney, breast, esophagus, pancreas, stomach, and liver. A wide morphologic spectrum of clinical appearances has been described in cutaneous metastases. This variable clinical morphology included nodules, papules, plaques, tumors, and ulcers. From a histopathologic point of view, there are 4 main morphologic patterns of cutaneous metastases involving the dermis, namely, nodular, infiltrative, diffuse, and intravascular. Generally, cutaneous metastases herald a poor prognosis. In this article, we review the clinicopathologic and immunohistochemical characteristics of cutaneous metastases from internal malignancies, classify the most common cutaneous metastases, and identify studies that may assist in diagnosing the origin of a cutaneous metastasis.**

Keywords: **Cutaneous metastasis, Metastasis, Malignancies, Skin metastasis.**

I. INTRODUCTION

Cutaneous metastasis can be the presenting sign of internal malignancies. The skin is a relatively uncommon site for metastasis from an internal malignancy with the reported incidence ranging from 0.7 to 10.4%. They may be found at any age but the greatest incidence is in the fifth to seventh decade [1]. These metastatic tumour deposits with a known primary malignancies are important for clinician and pathologists because of their variable clinical appearance, presentation and impact on morbidity, prognosis and treatment[2].Cutaneous metastasis is the first sign of extra-nodal disease in 7.6% and in general occurs in 0.7% to 9.0% of all cancer patients[3,4]. Incidence of various tumour metastasizing to the skin correlates with the sex-wise frequency of occurrence of various primary malignancies[3]. Breast carcinoma (69%) is the commonest cause of cutaneous metastasis in woman followed by carcinoma of large intestine (9%), lungs and ovaries (4%). Among men, primary site of carcinoma with cutaneous metastasis in decreasing order are the lungs(24%), large intestine(19%), oral cavity(12%), kidney and stomach(6% each)[5]. Here in we report four rare cases which proved to be metastatic deposits from visceral organs.

CASE 1:

A 50-year-old woman gradually developed multiple asymptomatic erythematous and edematous papules over the pubic area of two months duration (Fig. 1a). Six months before, she had developed an asymptomatic left inguinal lymph node enlargement in addition to night fever and sweating for which she received oral antibiotics without improvement.

Histopathological examination of skin lesions showed the presence of an atypical mononuclear cell infiltrate extending into the subcutaneous fat (Fig 1c). The infiltrate was composed of large cells with vesicular nuclei and prominent nucleoli

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as well as small lymphocyte-like cells (Fig 1d). The findings were consistent with anaplastic large cell lymphoma (ALCL). Immunostaining was positive for CD3, CD4, CD30, epithelial membrane antigen (EMA) (Fig. 1f) and negative for CD15 and cutaneous lymphocyte-associated antigen (CLA).

Lymph node biopsy showed effacement of nodal architecture by diffuse infiltrate of large malignant lymphoid cells with multinucleated giant cells (Fig. 1e). Foci of necrosis and microabscesses could be seen. Immunostaining for CD3, CD4, CD30 (Ki-1) was strongly positive.

An abdomino-pelvic computerized tomography (CT scan) revealed the presence of hepatosplenomegaly together with enlarged paraaortic and pelvic lymph nodes, especially at the inguinal, obturator and iliac regions. No other evidence of systemic involvement could be detected. The patient was staged as VIa T1 N3 M0.

Accordingly, the diagnosis of systemic form of Non-Hodgkin CD30+ve ALCL was made and treated with CHOP-MTX (cyclophosphamide, doxorubicin, prednisone, vincristine and methotrexate). Three weeks later, the skin lesions almost disappeared (Fig. 1b) and abdomino-pelvic CT scan showed marked decrease in the paraaortic and pelvic lymph nodes. There was No evidence of recurrence after 6 months of follow up.

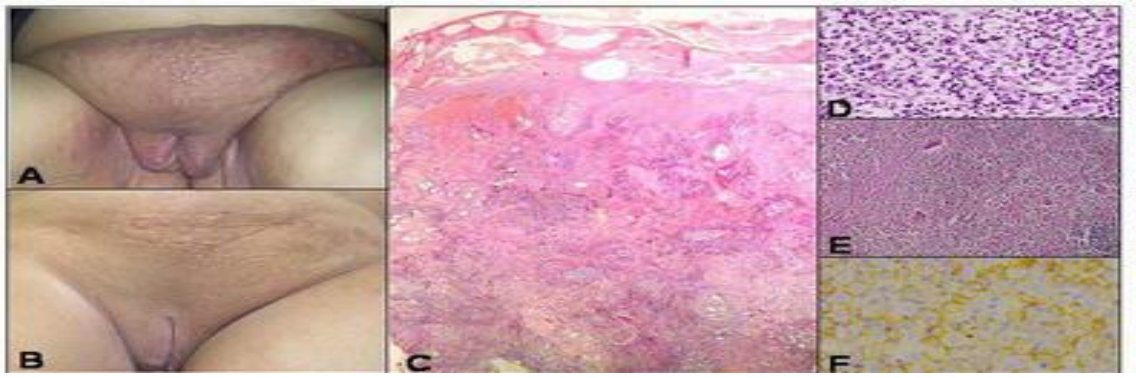

Fig 1: Skin metastases from CD30-positive ALCL (a) before and (b) after CHOP-MTX: (c) Atypical mononuclear cell infiltrate extending into the subcutaneous fat (HE, x100); (d) Infiltrate composed of large cells with vesicular nuclei with prominent nucleoli as well as small lymphocyte-like cells (HE, x400); (e) Lymph node biopsy showing diffuse infiltrate of large malignant lymphoid cells with multinucleated giant cells (HE, x100). (f) Positivity for CD3

CASE 2:

A 60 years male who presented with a small nodule on lower chest since 2 months was diagnosed as metastatic carcinoma on FNAC. CECT of the patient revealed metastatic growth in proximal stomach with multiple intrabdominal lymphadenopathy. Fifteen days later patient was operated and total gastrectomy with oesophagojejunal anastomosis was done. On histopathological examination it was diagnosed as carcinoma stomach. On immunohistochemistry HER2 and VEGF were strongly positive. Patient died on postoperative day 15

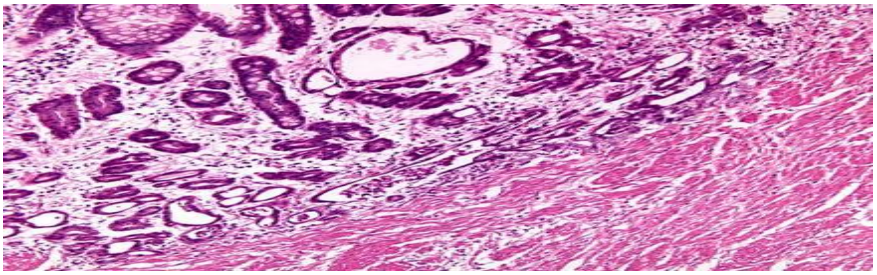

Fig 2. Gastric Adenocarcinoma at 10x Magnification

CASE 3:

A 62-year-old woman presented with multiple asymptomatic erythematous glistening papules on the front of the chest and abdomen and extending to the shoulders, buttocks and upper thighs of 3 months duration (fig. 3a). Four years before, the patient had been diagnosed as having invasive duct carcinoma of the right breast for which she had a modified radical mastectomy followed by radiotherapy.

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One year later, the patient was diagnosed as having invasive duct carcinoma of the left breast, which was also treated by modified radical mastectomy followed by radiotherapy. Histopathological examination of a skin papule showed invasion of the epidermis and dermis by malignant cells within a mucinous stroma indicating the presence of metastatic mucinous carcinoma (fig. 3b). Bone scan showed metastatic foci at the left side of the body of L4 and the posterior part of the left iliac crest (stage VI).

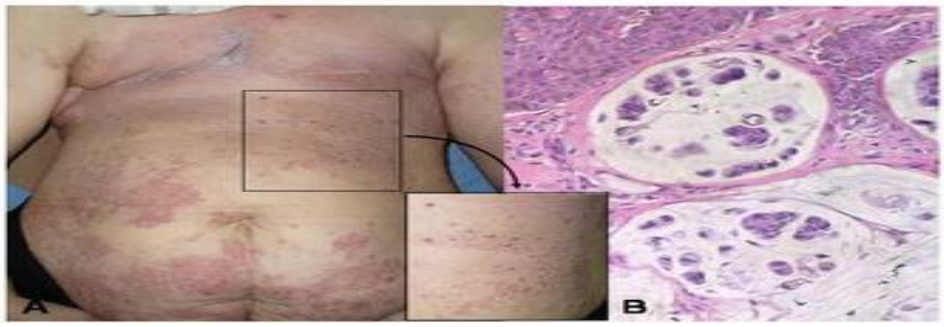

Fig 3: (a) Metastatic mucinous breast carcinoma; (b) Malignant cells within mucinous stroma invading the dermis (HE, x100)

CASE 4:

A 44-year-old male patient presented with multiple firm and tender nodules measuring 2-3 cm in diameter; some of which showed central black crust of 20 days duration (fig. 4a). Twelve months before, he had been diagnosed as a case of acute myeloid leukemia (AML) (M1-M2). At that time WBC count was 25000/mm3, Hb 11g/dl (13-16 g/dl) and platelets 170000/mm3 (normal range 200,000-400,000/mm3). Erythrocyte sedimentation rate was 130 mm/h and lactate dehydrogenase was 1225 IU/L (normal range 100-190 IU/L). A bone marrow biopsy showed hypercellularity, with myeloid and erythroid series showing dysplastic features, lymphocytes: 60% of absolute neutrophilic count (ANC), 20% blast cells, Plasma cells: 1% of ANC. Megakaryocytes were abundant. Myeloperoxidase (MP)-positive flowcytometry. CD33, CD13, CD34, CD15, and HLA DR were positive. Pelviabdominal ultrasonography showed hepatomegaly, bilateral renal stones, left hydroureter and hydronephrosis. The patient was treated with doxorubicin, cytarabine and etoposide every three months.

A skin biopsy showed little epidermal involvement with an underlying Grenz zone. A deep dermal monocytic infiltrate reaching the subcutaneous tissue was present. The infiltrate was accentuated perivascularly and periadnexally. The cells were large with an oval, vesicular nucleus and hyperchromatic basophilic cytoplasm (fig. 4b). Collagen fibers separated by leukemic cells (Indian filing) were evident in some areas (fig. 4c).

Immunostaining for CD34, CD68 was positive confirming the diagnosis of leukemia cutis.

On presentation of skin lesions the general condition of the patient worsened with a CBC showing Hb: 6.9 gm/dl, WBCs: 21000/mm3, PTL: 22000/mm3, RBCs: 173 mg/dl, LDH: 800. The patient died within two months of appearance of skin lesions.

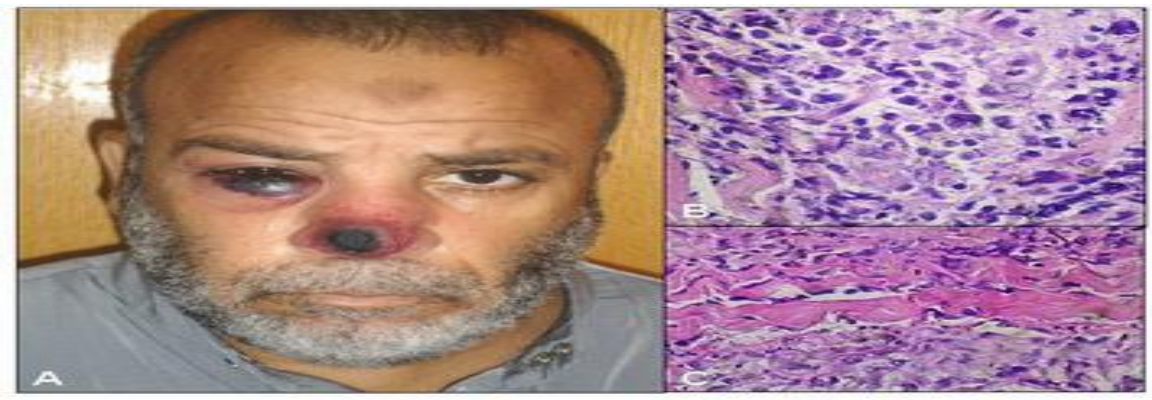

Fig 4: (a) Leukemia cutis in a patient with AML; (b) Pleomorphic monocytic cells with an oval, vesicular nucleus and basophilic cytoplasm (HE, x400); (c) Collagen fibers separated by leukemic cells (Indian filing) (HE, x400)

II. DISCUSSION

The occurrence of cutaneous spread of internal malignancy is rather rare, however the incidence of malignancies is rapidly increasing and it is likely that skin metastases will be more frequently encountered [6]. Such metastases offer an easily accessible tissue sample for rapid histopathological diagnosis of the malignancy and response of cutaneous metastatic lesions to chemotherapy mirrors the response of the primary tumor. A thorough clinical examination of the skin for any metastasis is therefore mandatory for a patient with any type of cancer.

The triad of unexplained fever, inguinal lymphadenopathy, and skin lesions is highly suspicious for lymphoma as shown in case one in this report. Histopathological and immunohistochemical examination of skin and lymph node biopsies were consistent with the diagnosis of CD30 positive ALCL of the skin together with malignant regional lymph node involvement. Although the primary cutaneous form of ALCL is defined by skin-only involvement without systemic dissemination at presentation, draining regional lymph node involvement occurs in approximately 25% of patients with only skin lesions. Whether the patients only showing draining regional lymph node involvement, as in our case, should be considered to have a primary cutaneous or systemic form remains controversial [7]. Primary cutaneous cases are reported to lack EMA and Anaplastic Lymphoma Kinase (ALK) but express CLA [8], whereas ALCL that present with systemic extracutaneous disease (with or without skin involvement) are CLA- and EMA/ALK+ in 60% of cases [9].

The differentiation of primary cutaneous and systemic disease is of great prognostic value. The 5-year survival rate of the former is 90% with occasional spontaneous regression (up to 25% of cases) of the skin lesions. The prognosis of the systemic form with secondary cutaneous involvement depends on the expression of the ALK protein. Patients with expression of ALK have a 5-year survival rate ranging from 70-80%, while survival ranges from 15-30% without ALK expression [10]. ALK positive cells are usually also positive for EMA [11]. Our case was CLA - but EMA+ indicating that it is a systemic form of ALCL with a good prognosis. The skin lesions were the first manifestation of the underlying malignancy and their resolution with treatment was a valuable indicator of the response of the primary malignancy to therapy.

A solitary cutaneous nodule could be the first evidence of a metastatic disease in a known patient with systemic ALCL previously treated successfully as shown in the second case. Indeed, it is a good example of metachronous metastases, i.e., metastases developing years after the diagnosis and treatment of the primary malignancy.

Because breast cancer is so common, cutaneous metastases are the most frequently encountered type in women in most clinical practices. Cutaneous involvement from breast carcinoma preferentially occurs in the skin overlying or proximal to the area of the primary tumor by direct extension or through lymphatic vessels. Nodular carcinoma, inflammatory or erysipeloides carcinoma, telangiectatic and "en cuirasse" carcinoma are the typical clinical manifestations of the lymphatic dissemination to the skin [5]. The patient in this report had cutaneous metastatic mucinous carcinoma clinically evident as an erythematous glistening (due to mucinous content) papular eruption, which was found to be a part of systemic metastatic disease. Mucinous carcinoma accounts for 3% of breast cancers and is more common among older women. This rare type of invasive breast cancer is formed by mucin-producing cancer cells and carries a better prognosis than the more common types of invasivebreast cancer. Colloid carcinoma is another name for this type of breast cancer [12].

Acute myelogenous leukemia (AML) shows the second highest rates of leukemia cutis after adult T-cell leukemia/lymphoma. In general, leukemia cutis is a poor prognostic sign. It has been shown that in the presence of leukemia cutis in AML or chronic myeloid leukemia, the disease course is aggressive and the length of survival is short (7.5 and 9.4 months respectively) [13]. Baer et al. showed that 90% of patients with AML and leukemia cutis had other sites of extramedullary involvement. In case 4 the appearance of skin lesions in a patient with AML was associated with a rapid decline in blood indices and death within 2 months despite the initial improvement [14].

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